Title

Rationale and design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: A comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter ser...

Authors

Lee, Sang-Eun
Chang, Hyuk-Jae
Rizvi, Asim
et al.

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Full Title: Rationale and Design of the PARADIGM Trial: Comprehensive Exploration of Plaque Progression and Its Impact on Clinical Outcomes: Multi-center Serial Coronary Computed Tomography Angiography Study

Short Title: Rationale and Design of the PARADIGM Trial

Sang-Eun Lee[1], Hyuk-Jae Chang[1], Asim Rizvi[2], Martin Hadamitzky[3], Edoardo Conte[4], Daniele Andreini[4], Gianluca Pontone[4], Valentina Volpato[4], Ilan Gottlieb[5], Matthew J. Budoff[6], Filippo Cademartiri[7], Erica Maffei[7], Hugo Marques[8], Jonathon Leipsic[9], James K. Min[2]

[1] Division of Cardiology Severance Cardiovascular Hospital, Integrative Cardiovascular Imaging Center, Yonsei University Health System, Seoul, South Korea

[2] Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and Weill Cornell Medical College, New York, New York

[3] Division of Cardiology, University of Munich, Munich, Germany,

[4] Centro Cardiologico Monzino, IRCCS, Milan, Italy

[5] Department of Radiology, Casa de Saude São Jose, Rio de Janeiro, Brazil

[6] Department of Medicine, Harbor UCLA Medical Center, Los Angeles, CA, USA

[7] Department of Radiology, University Hospital of Parma, Parma, Italy

[8] Hospital da Luz, Lisbon, Portugal

[9] Department of Radiology, St Paul's Hospital, University of British Columbia, Vancouver, Canada

Address for Correspondence:

Hyuk-Jae Chang, MD

Division of Cardiology Severance Cardiovascular Hospital

Integrative Cardiovascular Imaging Center

Yonsei University Health System

50-1 Yonsei-ro Seodaemun-gu Seoul, 120-752 South Korea

Email: hjchang@yuhs.ac

James K. Min, MD

Dalio Institute of Cardiovascular Imaging

New York-Presbyterian Hospital and Weill Cornell Medical College

413 E. 69th Street, Suite 108

New York, NY 10021

Email: jkm2001@med.cornell.edu

ABSTRACT

BACKGROUND: The natural history of coronary artery disease (CAD) in patients with low to intermediate risk is not well characterized. Earlier invasive serial studies have shown the progression of atherosclerosis burden, but they were mostly focused on high-risk patients. The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging) registry is a large, prospective, multinational dynamic observational study of patients undergoing serial CCTA. The primary aim of PARADIGM is to characterize the natural history of mild to moderate CAD in relation with its impact on clinical outcomes.

METHODS: The PARADIGM registry represents ____ consecutive patients at 9 cluster sites in 7 countries. PARADIGM sites were chosen on the basis of adequate CCTA volume, site CCTA proficiency, and local demographic characteristics and medical facilities to ensure a broad-based sample of patients. Patients with suspected but without known CAD being referred for clinically indicated CCTA will be followed and enrolled if they had a second CCTA scan. Patients are followed up after serial CCTA performance to identify adverse CAD events, including death, myocardial infarction, unstable angina, target vessel revascularization, and CAD-related hospitalization.

CONCLUSIONS: The results derived from the PARADIGM registry will add incremental and important insights into changes in CCTA findings in accordance with progression of CAD that confer prognostic value beyond demographic and clinical characteristics.

INTRODUCTION

Ischemic heart disease remains the most important cause of morbidity and mortality worldwide.[1] At present, the development of the atherosclerotic lesion in the vessel wall is conceptualized as a sequential event,[2] that the progression of atherosclerosis in the coronary artery lead to stenosis or plaque rupture and eventual myocardial damage. However the temporal evolution of progression has rarely been serially monitored or visualized.

Previous clinical trials demonstrated an effect of statin therapy on a population level.[3] Statins, supposedly by stabilizing the atherosclerotic plaque, were effective in reducing cardiovascular disease events rates. However, assessment of treatment response has been inferred by cholesterol monitoring, not by individualized direct imaging of the plaque due to limitation in noninvasively monitoring the diseased vessel wall. Direct visualization of serial changes in plaque and vessel wall may help understanding the natural history of disease progression and the response to therapy, and eventually will help managing patients more efficiently.

To date, the progression or change in response to medical therapy of coronary plaque has been demonstrated mainly by invasive techniques including quantitative coronary angiography[4,5] or intravascular ultrasound (IVUS).[6-8] However, the invasiveness of these methods limits their use to patients who are undergoing invasive coronary angiography (ICA). As a result, most of studies so far have been focused on the patients with acute coronary syndrome (ACS) or high risk of coronary artery disease (CAD), which consist only a small portion on population level. Thus, in the majority of patients with suspected with CAD who have low to moderate risk and therefore not

eligible for ICA according to current guideline,[9,10] the natural history, including sequential changes in plaque morphology or composition is not well characterized.

Further, prior studies examining plaque progression have been primarily restricted to measures of obstructive CAD on a per-lesion basis,[4-8,11] and non-ischemic lesions or newly developed lesions on a follow-up are largely neglected. This strategy also limited our understanding in progression of mild lesion or development of atherosclerotic plaques, despite the fact that non-ischemic lesions are also found to be associated with development of future ACS in recent studies.[12-14] To understand the progression of atherosclerosis of coronary arteries fully, assessment of CAD should cover the whole coronary tree, which is hard when using invasive techniques.

In addition, most available studies assessed the progression of plaque by invasive procedures have included fewer numbers of patients or used a relatively shorter-term follow-up to apply on population level.[4-8,15] Although large number of patients were enrolled in some studies using quantitative coronary analysis, the traditional reference method for assessing the severity of CAD,[16,17] limitations of this technique including the underestimation of disease severity and inability to assessing the changes in vessel wall are well known.[18,19]

Recent developments in coronary computed tomography angiography (CCTA) enable not only detection of luminal narrowing but also characterization of high-risk plaque morphology[20] and quantification of plaque volumes.[21-24] The relationship of CCTA-defined increasing burden of CAD and cardiovascular risk has been reported in the CONFIRM registry.[25] Further, more recent studies have used fully or semi-automated plaque assessment, thereby allowing higher accuracy and better

reproducibility than manual technique.[21,26,27] In addition, the relatively high radiation dose, which was a prior limiting factor of serial CCTA examination, have significantly been reduced from 15 to 20 mSv to below 1 mSv in selected patients.[28] Hence, CCTA has emerged as an effective alternative to invasive IVUS in serial studies for assessment of interval change in morphological plaque characteristics and efficacy of treatment, especially in patients with flow-limiting lesions.

The PARADIGM registry has been developed to directly address the natural history of coronary atherosclerosis, characteristics and the determinants of coronary plaque progression, and to define the impact of plaque progression in terms of clinical outcomes in patients with mild to moderate CAD. This report describes the rationale and design features of the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging) registry.

OVERALL STUDY DESIGN

The PARADIGM Trial (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) is a prospective, open-label, international, multicenter dynamic observational registry designed to evaluate associations between changes in serial CCTA imaging findings and clinical presentation and their ability to predict mortality and major adverse cardiac events (MACEs) in patients with mild to moderate CAD. The registry uses a collaborative design using contribution and merger of similar prospectively enrolled cohorts from 16 sites around the world. Patients who had CCTA will be prospectively followed, and among them, patients with a second CCTA scan will be enrolled. The change in plaque composition,

size, lumen dimensions, and arterial remodeling will be assessed along with association with clinical outcomes. Qualifying sites participated in data collection and common data analysis if the site collected data including clinical presentation, risk factors, CCTA data recordings, and follow-up data including all-cause mortality and MACEs.

STUDY OBJECTIVES

Primary Objective

The primary objective of the PARADIGM study is to describe the natural history of the coronary atherosclerotic plaque development and progression in mild to moderate CAD over time by CCTA with demographic and clinical data for refinement of risk stratification of patients with suspected CAD.

Secondary Objectives

Secondary objectives will include following: (1) to determine the most optimal and effective way to define the progression of plaque assessed by serial CCTA; (2) to find the determinants of plaque progression; (3) to evaluate the prognostic power of changes in CCTA findings in specific subgroups, including but not limited to women, diabetics, dyslipidemia, and different ethnic groups; (4) to find the imaging parameters derived from serial CCTA that can be used in monitoring the patients with CAD; (5) to associate changes in serial CCTA findings with clinical risk factors and symptoms for development of a CCTA global risk score for patients with suspected CAD; and (6) to test the efficacy and rationality of using CCTA imaging indicators as a surrogate marker of atherosclerosis progression.

TARGETED POPULATION

The PARADIGM target population is patients with suspected but not known CAD who had undergone serial CCTA by physician referral. Sites that had collected cohorts of CCTA patients with symptoms, risk factors, CCTA image data, and outcomes were invited to contribute data for a merged database. This sample includes patients with suspected but without known CAD, and asymptomatic subjects undergoing CCTA for risk stratification to evaluate the significance of changes in CCTA findings in different clinical contexts.

STUDY ENDPOINTS

The primary endpoint of the PARADIGM registry is a change in plaque composition and plaque progression or regression detected by follow up CCTA. Secondary endpoints of PARADIGM include MACEs, inclusive of cardiac mortality, myocardial infarction, unstable angina requiring hospitalization, and revascularization.~~composite of MACE, inclusive of the following: death, non-fatal myocardial infarction, unstable angina (including new onset angina or those requiring hospitalization, those requiring revascularization, or patients who are troponin-positive), urgent or emergent coronary revascularization.~~

ELIGIBILITY CRITERIA

Patient Eligibility Criteria

All consecutive patients undergoing CCTA of 64-detector rows or greater at cluster sites are included within the PARADIGM registry if all inclusion criteria were met. Patient inclusion criteria include the following: (1) patients underwent two or more clinically indicated CCTA with 64-detector rows or greater for CAD evaluation, (2) at least 2 year interval between the baseline and follow-up CCTA, (3) no documented CAD at baseline, and (4) prospective data collection for CAD risk factors. No explicit patient exclusion criteria were defined.

Exclusion criteria includes (1) unavailable either clinical or laboratory data within 1 month from index CCTA or follow-up CCTA, (2) patients with prior revascularization before the index CCTA, and (3) poor image quality of CCTA.

Site Eligibility Criteria

The site requirements for participating sites of the PARADIGM registry are as follows: (1) >200 patients per annum undergoing CCTA by 64-detector rows or greater, (2) incorporation of CCTA into daily clinical practice by members of the medical center other than those involved with the CCTA performance and interpretation, and (3) director of laboratory possessing level III-equivalent expertise in CCTA.

STUDY SITES/PARTICIPATING CENTERS

During the initial phase of the PARADIGM registry, 9 cluster sites contributed data from patients undergoing CCTA of 64-detector rows or greater. Seven countries in North America, Europe, South America and Asia are presently represented in this multinational effort, including the United States, Canada, Italy, Germany, Brazil,

Portugal, and South Korea. Data collection activities began in 2013 with a goal of collecting data on approximately 3000 patients.

The geographic clusters were selected to represent medical centers of different sizes and with different diagnostic capabilities, patient populations with diverse clinical and demographic characteristics. Medical centers where CCTA has been incorporated into daily clinical cardiac practice were chosen. Each site principal investigator was required to obtain approval from the local ethics committee or institutional review board.

Sites were eligible for merger into the PARADIGM registry if they performed prospective cohort collection of CCTA findings with >80% overlap with the predefined data dictionary. Databases had to include uniform collection of major categories of patient data, including demographics, history of prior CAD, Framingham risk factors, symptom indication for CCTA, raw image dataset of CCTA, and obtained follow-up data for all-cause mortality for ≥2 year with <5% loss to follow-up. Sites were allowed to provide both previously published and unpublished data.

PATIENT RECRUITMENT AND EVALUATION

All PARADIGM study patients underwent initial and follow-up CCTA based on order from their primary physician. Demographic data, targeted medical history, cardiovascular risk factors, and laboratory data was prospectively collected in electronic case report forms (eCRFs) at the time of the initial CCTA and at the time of follow-up CCTA. **(Table 1)**

Standardized definitions for cardiovascular risk factors were used. Medical history including previous stroke, TIA, peripheral artery disease was documented. If the

patients had chest pain, it was recorded as one of follows: atypical chest pain, noncardiac chest pain, or typical chest pain. (Fig. 1).

PATIENT FOLLOW-UP

Patient follow-up is performed by each local center by a dedicated physician or research nurse or both. All patients were followed for a primary endpoint of composite MACEs. Ascertainment of death was determined by direct interview, telephone contact, or review of medical records.

The PARADIGM database will be locked in ____, and will be reopened every ___ months to add additional investigative sites' data and to update preexisting sites for longer follow-up evaluation.

ACQUISITION AND INTERPRETATION OF CCTA

All testing, image acquisition, and image post processing for CCTAs in the PARADIGM cohort are in direct accordance with SCCT guidelines.[29,30] No restrictions were placed regarding the type of CT scanner or type of iodinated contrast, except the performance of CCTA should be done by a scanner with ≥ 64-detector rows. As a consequence, scanner type differed by center. Data about method of electrocardiographic gating, defined as either retrospective helical gating or prospective axial triggering and CCTA scan parameters including tube current (mA), tube voltage (kV), dose-length products, and overall study quality (denoted as excellent, satisfactory, or poor) were recorded.

Datasets (baseline and follow-up) from each contributing centers will be transferred to an offline workstation for analysis using semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9, Medis Medical Imaging Systems, Leiden, The Netherlands). Independent level III–experienced readers blinded to clinical and test results will analyze all of the CCTAs. Both qualified and quantified analysis will be done on a per-patient, per-vessel, and per-lesion level.

The major vessels (left anterior descending artery, left circumflex artery, and right coronary artery) were considered for analysis using the modified 17-segment American Heart Association model for coronary segment classification.[31] Lesions were matched between baseline and follow-up CCTA using branch points as landmarks.

The presence of coronary atherosclerosis is defined as any tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.

For qualitative analysis, the presence of positive remodeling, low attenuated plaque, and spotty calcification will be identified, and plaque type will be recorded as one of the followings: noncalcified, calcified, or mixed calcified plaques. A remodeling index is defined as a maximal lesion vessel diameter divided by proximal reference vessel diameter, with positive remodeling defined as a remodeling index ≥1.1. Low attenuated plaque is defined when any voxel <30 Hounsfield units within a regions of interest and spotty calcification is defined by an intra-lesion calcific plaque <3 mm in length that comprised <90° of the lesion circumference.[20] Percentage of obstruction of coronary artery lumen is based on a comparison of the luminal diameter of the segment exhibiting obstruction to the

luminal diameter of the most normal-appearing site immediately proximal to the plaque. Diameter stenosis severity was graded as none (0%), very mild (1-24%), mild (25-49%), and moderate (50-70%).

For quantitative atherosclerotic plaque analysis, a semi-automated method will be utilized which has been validated versus IVUS in previous studies[26]. First, a centerline originating from the ostium defined by the observer will be automatically drawn. Then stretched multi-planar reformatted images will be generated, and the lumen and vessel borders will be detected longitudinally in 4 different cut planes by the software and will be corrected by observer if necessary. Based on these longitudinal contours, cross-sectional images at 0.5 mm intervals will be calculated to create transversal lumen and vessel wall contours. The settings for window level and width will be fixed at 740 HU and 220 HU, respectively.

To detect the progression or development of a plaque over time more efficiently, no gap method[32,33] will be used, assuming that there is no gap between vessel wall and lumen except where a plaque exist, instead of drawing each line separately throughout whole vessel. **(FIGURE 1)**

Plaque volume is defined as the difference between vessel volume and lumen volume, and mean plaque burden is calculated as plaque volume/vessel volume x 100 (%).

IMAGE REPOSITORY

All CCTA images will be sent to a core laboratory for image analysis. The core laboratory will perform qualitative and semi-quantitative analysis for accuracy of CCTA.

CCTA Core Laboratory interpretation will be employed for post-hoc analysis. Images will be stored either by web-based server or locally by a single informatics core laboratory site.

DATA MANAGEMENT

Completed eCRFs will be entered by sites and checked locally for possible errors or omissions. A clean dataset will be transmitted to a central data repository at the Clinical and Data Coordinating Center (CDDC) for merge with other sites' datasets. On receipt, the CDCC will perform an additional check for possible errors, omissions, or out-of-range values.

The CDCC will qualify all investigators by determining the following: knowledge and experience level with standard-of-care CCTA scanning and ICA procedures; adequate patient population to enroll within the scheduled timeline; and the presence of an established clinical research department. Completion of these requirements will be documented via a site qualification questionnaire or equivalent, along with documentation of investigator experience and background.

DATA ANALYSIS

Descriptive, univariate, and multivariate analyses will be conducted. For the primary objectives, variables that showed significant relationships in previous studies and those with a p value <0.1 in the univariate Cox proportional hazards models will be defined as related variables, and those will be included in multivariable Cox proportional hazard analysis to evaluate the association of changes in CCTA and clinical variables.

Cutoff values for progression group will be determined based on receiver-operator characteristic (ROC) curves. The sensitivity and specificity value will also be calculated.

In per-lesion and per-vessel analysis, continuous variables between groups will be analyzed using an independent t-test, while those between categorical variables will be analyzed using a chi-square test. Changes in lesion characteristics will be analyzed using mixed linear model.

DISCUSSION

The PARADIGM registry is a prospective international multicenter observational cohort registry, which aims to describe and characterize the natural history of coronary atherosclerosis in patients with low to intermediate risk, and further, to find the determinant of the disease progression. The result of this trial will inform the clinicians about the clinical and pathological course of CAD and will guide their clinical decisions on managing patients using changes in CCTA as a surrogate marker of disease progression.

Previous studies using invasive techniques[34-37] have identified high-risk features such as thin-cap, low residual lumen area, and spotty calcification as the hallmark of high-risk plaques. These high-risk plaques identified by either IVUS or OCT were also associated with adverse clinical outcomes.

However, since all these invasive procedure-based studies were naturally performed on patients considered high risk or those with previous ACS, there is a limitation as to how to directly apply their results to patients with mild to intermediate risk. In patients with subclinical CAD, the probability of finding these high-risk plaques is

low, and therefore these techniques are not suitable to be used as an indicator of disease progression. Moreover, it has been conceived that atherosclerotic CAD is a generalized disorder with a dynamic nature of plaque morphology, and that therapeutic intervention for atherosclerosis is most effective when started at an early stages of the disease.[38] Therefore, rather than simply characterizing and identifying the presence of such coronary atherosclerotic plaques as high risk, quantitative assessment of disease burden and progression has remained a subject of intense interest.

The ability of CCTA to noninvasively image plaque composition as well as assessment of the entire coronary tree wall thickening enables detection and monitoring of earlier stages of CAD.[39,40] It has been also hypothesized that noninvasive imaging modalities such as CCTA further stratify intermediate risk patients to a very high risk group.[41,42] Moreover, in IVUS and MSCT comparative studies,[24,43,44] CCTA was been shown to accurately evaluate atherosclerotic plaque size, remodeling, eccentricity, and plaque composition. Based on the small mean differences between CCTA and IVUS with virtual histology measurements, it was suggested that quantitative CCTA analysis could be acceptably used on a population level.[44] More recent studies using QCA or IVUS-like parameters also validated the reliability and reproducibility of CCTA in quantitative assessment of coronary atherosclerotic plaque.[26,27,33,45]

Still, there is limited data regarding plaque progression using CCTA. Although some papers have used serial CCTA findings to describe the progression or change in coronary plaques,[33,45-51] research to date has been limited by a small study sample, relatively short time of interval between the scans, as well as focus on a specific subset of patients or lesions. Also, these studies have primarily focused on high-risk

populations **(TABLE 2).** Moreover, there had been no consensus on optimized methodology on how to quantify the plaque volume by CCTA to provide reproducible and standardized results.

In order to thoroughly understand the natural history of atherosclerotic CAD, and to optimize the CCTA methodology and clarify the role of CCTA in quantitative assessment of CAD, prospective studies of low to moderate risk populations are definitely needed. Noninvasive imaging methods such as CCTA with ability to accurately estimate change in disease burden over time is critical to assess the response to medical treatments and to monitor the disease process. The PARADIGM trial is designed specifically to answer these questions.

The PARADIGM registry will be the first to address the utility of quantitative assessment of disease burden using serial CCTA in populations with low to moderate risks, using its large database collected from geographically diverse, representative of persons who are presently undergoing clinically indicated CCTA.

Further, the results of this trial may allow for contemporary revision of indications of CCTA and its role in monitoring patients with suspected CAD. Current guidelines worldwide do not recommend serial CCTA, however results derived from the PARADIGM may prove that direct visualization of the lesion maybe adequate in monitoring patients with mild to moderate disease.

NEW KNOWLEDGE GAINED

Direct visualization of natural history of atherosclerosis and identification of clinical determinant of plaque progression or regression holds the potential to shift the

paradigm of CAD monitoring for patients with suspected CAD with mild to moderate risks, with aims of offering earlier therapeutic strategies thereby preventing disease progression and improving clinical outcomes. We believe that the PARADIGM registry is properly designed to answer these important questions in the most suitable manner.

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Table 1. Clinical variables

Age, years, mean ± SD	
Interval between CCTA, mean ± SD	
Follow-up time, years, mean ± SD	
Male, n (%)	
Family history of CAD, n (%)	
Hypertension, n (%)	
Diabetes mellitus, n (%)	
Dyslipidemia, n (%)	
Active smoker, n (%)	
Number of risk factors	
Medications	
Beta blockers	
CCB	
Diuretics	
ACEi/ARB	
Statins	
Oral hypoglycemic agents	
Insulin	
Antiplatelet agents	

Table 2. Previous studies using serial CCTA

Reference	Moda-lity	patients		Interval between scans	Design	Findings
		n	inclusion			
Burgstahler et al. 2007[49]	CCTA	46	Elevated CAD risk	1.3 y	Prospective atorvastatin	24% NCPV regression in statin therapy
Hoffmann et al. 2010[46]	CCTA	63	Clinically indicated	25 m	Retrospective	38% increase in NCPV
Inoue et al. 2010[47]	CCTA	32	Clinically indicated	12 m	Prospective observational	PV & LAP regression in statin therapy
Papadopoulou et al. 2012[33]	CCTA	32	ACS	39 m	Prospective observational	Normalized atheroma volume increased by 47 mm^3 (6.7%)
Zeb et al. 2013[45]	CCTA	100	No Hx of CAD	1.1 y	Retrospective	28% decrease in NCPV
Lo et al. 2015[48]	CCTA	40	HIV pt with subclinical CAD	1 y	Prospective randomized	4.7% plaque volume regression in statin therapy
Lehman et al. 2009[50]	CCTA	69	Acute chest pain in ER	2 y	Prospective	Semiquantitative method 12.7% increase in number of slices with plaque
Motoyama et al. 2015[51]	CCTA	449 (sub-analysis)	Clinically indicated	1 y	Retrospective cohort	No quantitative assessment

ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ER, emergency room; Hx, history; HIV, human immunodeficiency virus; LAP, low attenuated plaque; MLA, minimal lumen area; MLD, minimal lumen diameter; NCPV, non-calcified plaque volume; PR, positive remodeling; PV, plaque volume

Figure 1. Representative figure of assessment method of CCTA